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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,137	08/17/2005	Rian Van Meeteren	Q84960	6831

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 12/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,137	VAN MEETEREN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 17 August 2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 are presented for examination.

Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/JP03/07149, filed June 5, 2003, which claims priority under 35 U.S.C. 119(a-d) to Japanese Patent Application No. 2002-166408, filed June 7, 2002. Applicant's Information Disclosure Statement (IDS) filed August 17, 2005 has been received and entered into the application. As reflected by the attached, completed copy of form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Applicant's Claim for Priority Under 35 U.S.C. 119(a-d)

Applicant's request to afford the present application the benefit of the filing date of PCT Application No. PCT/JP03/07149, filed June 5, 2003, of which the present application is a proper National Stage (371) entry, has been granted.

Receipt of the certified copy of Japanese Patent Application No. 2002-166408, submitted under 35 U.S.C. 119(a)-(d), has been placed of record in the file.

Accordingly, in the absence of a translation of Japanese Patent Application No. 2002-166408, prior art that became publicly available during the intervening period between the filing date of the PCT application and the filing date of the Japanese Patent Application may be applied. Applicant is reminded that a translation of the Japanese Patent Application can be furnished to the Office in order to overcome such a rejection.

Claim Rejection - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5-6 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of overactive bladder occurring in the presence of a pathological factor (e.g., bladder outlet obstruction or the like), does not reasonably provide enablement for the treatment of overactive bladder appearing in the absence of a pathological, neurological or metabolic factor that would account for the presence of such a condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The present claims directed to a pharmaceutical composition are properly included in the present rejection as directed by the MPEP at §2164.01(c), which states, "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)." Thus, the instant rejection made under 35 U.S.C. 112, first paragraph, is proper as it is applied to present claims 1-4 because the claims are drawn to a composition "for the therapy of overactive bladder" (see present claim 1, for example).

1 and 2) The claimed invention is directed to a pharmaceutical composition comprising tamsulosin or pharmaceutically acceptable salts thereof, optionally in combination with a muscarinic receptor antagonist, such as quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate or pharmaceutically acceptable salts thereof. The

invention is further directed towards a method of treating overactive bladder comprising the administration of tamsulosin or pharmaceutically acceptable salts thereof, optionally in combination with a muscarinic receptor antagonist, to a patient.

3 and 7) Overactive bladder is known in the prior art as a complex condition that may be caused by a number of factors, such as the neurologic disorders of stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy or spinal cord lesions, or other non-neurological abnormalities, such as bladder stones, muscle disease, urinary tract infection or drug side effects. In addition, overactive bladder can also arise without apparent cause (i.e., idiopathic).

However, the fundamental physiologic cause of overactive bladder is not known. Landau et al. states, "Due to the enormous complexity of micturition (the act of urination), an exact mechanism which causes overactive bladder is not known." (see Landau et al., U.S. Patent Application Publication No. 2005/0272719; 2005) Current, conventional therapies for the treatment of overactive bladder include medication, diet modification, bladder training, electrical stimulation or surgery. In particular, overactive bladder is amenable to therapy when the apparent cause can be identified and treated and, thus, the symptoms are reduced and/or ameliorated.

In cases where there is no apparent cause, i.e., where overactivity of the bladder appears without any pathological or neurological condition that would contribute to such a condition, the predictability of treatment using such conventional therapies significantly decreases. In the absence of a pathological condition causing overactivity of the bladder, such as, for example, benign prostatic hypertrophy, wherein the enlarged prostate increases pressure on the bladder

muscle, causing instability and, thus, feelings of urgency and frequency, treatment of such a condition can only be achieved by targeting the physiological "mechanism" (i.e., nerve conduction via the central or peripheral nervous system, etc.) by which such a condition results.

The art has proposed various abnormalities in peripheral or central mechanisms from which overactive bladder results (see Landau et al., paragraphs [0006-0007]). However, due to the sheer number of mechanisms that have been attributed, even remotely, to the development of overactive bladder raises the question that certain commonly accepted treatments for overactive bladder may not have the same efficacy in treating idiopathic overactive bladder as they would in treating overactive bladder resulting from a substantive, pathophysiological abnormality.

In light of such and, further, given that the art recognizes the highly complex nature and poor understanding of overactive bladder, the contention that the administration of a single active agent, such as tamsulosin, or a combination of agents, such as tamsulosin in combination with a muscarinic receptor antagonist, for the treatment of idiopathic overactive bladder (i.e., in the absence of a pathological, neurological or metabolic factor contributing to such a condition) would have been sufficiently unusual that adequate data would need to be shown in support of such an assertion. As stated previously, because absolute success is not reasonably possible with most diseases or disorders, especially a condition as highly complex as overactive bladder without apparent pathological, neurological or metabolic cause, the specification, which lacks an objective showing that such could be effectively treated, is viewed as lacking an enabling disclosure of the same.

4, 5 and 6) Applicant expressly defines overactive bladder as the "medical condition referring to the symptoms of frequency and urgency, with or without urge incontinence, when

appearing in the absence of local pathological, neurological or metabolic factors that would account for these symptoms." (see page 6, paragraph 3)

The specification at pages 17-26 only provides one substantive example demonstrating the efficacy of tamsulosin hydrochloride or tamsulosin hydrochloride in combination with solifenacin succinate (corresponds to Applicant's presently claimed muscarinic receptor antagonist of claim 4) in rats with bladder outlet obstruction. Such an obstruction is considered to be a pathological factor that would contribute to the symptoms and conditions that characterize overactive bladder. The specification, however, lacks any exemplary data showing the efficacy of the agents in overactive bladder without apparent cause. In light of the fact that Applicant has specifically defined and, thus, excluded the treatment of overactive bladder insofar as it results from some pathological or neurological or metabolic factor, such an example is not considered to be representative of the efficacy of the presently claimed active agent(s) in the treatment of overactive bladder in the absence of any contributing pathological condition. In other words, such data is not commensurate in scope with the claimed subject matter. Furthermore, such an example is not adequate disclosure to support the synergistic, i.e., greater than additive, activity of the agent tamsulosin in combination with a muscarinic receptor antagonist in treating overactive bladder in the absence of a pathological condition, since Applicant has merely demonstrated synergy of the agents in treating overactive bladder as it results from bladder outlet obstruction (i.e., a pathological factor).

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of overactive bladder,

particularly overactive bladder without pathological cause, there is no apparent data to support the contention that the use of the claim specified active agent(s) had efficacy in treating overactive bladder in the absence of pathological factors, since the present specification lacks such enabling disclosure. Without such direction, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the present invention.

8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the treatment of overactive bladder appearing in the absence of local pathological, neurological or metabolic factors, could be achieved using the presently claimed composition of tamsulosin or salts thereof, optionally in combination with a muscarinic receptor antagonist, given the disclosure and the supporting examples provided in the present specification.

For these reasons, claims 1-8 fail to meet the tenor and express requirements of 35 U.S.C. 112, first paragraph and are, thus, properly rejected.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I Claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 5-6 provides for the use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for overactive bladder, which may be used in combination with a muscarinic receptor antagonist, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

For this reason, claims 5-6 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination and the application of prior art, claims 5-6 will be interpreted to read upon a method for treating overactive bladder via the administration of a therapeutically effective amount of tamsulosin, which may also be administered in combination with a muscarinic receptor antagonist.

II Claims 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

For example, claim 3 recites a pharmaceutical composition according to claim 1 or claim 2, wherein "said composition contains muscarinic receptor antagonist" (see line 3 of claim 3). Such language renders the claim indefinite because it is not clear whether Applicant intends the

composition to *further comprise* a muscarinic receptor antagonist in combination with tamsulosin, or whether the composition *only* contains muscarinic receptor antagonist.

Although it is noted that the claims are read in light of the specification, it remains that the language in the claims does not expressly and specifically set forth that which Applicant regards as the invention and that for which Applicant is seeking protection.

For this reason, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

III Claims 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The claims are drawn to a method for treating overactive bladder by the administration of tamsulosin or a pharmaceutically acceptable salt, or tamsulosin or a pharmaceutically acceptable salt in combination with a muscarinic receptor antagonist, but fail to define the host in whom such a compound or combination of compounds is to be administered. For example, it is unclear whether Applicant intends the host to be a patient in need of overactive bladder treatment or *any* subject.

For this reason, claims 7 and 8 are not considered to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph and are, thus, properly rejected.

It is suggested that Applicant amend the claims to define the host in whom the presently claimed method of treatment is to be practiced. Applicant is reminded, however, that such an amendment do not necessarily equate to the claims being free of the cited prior art.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshinaga (EP 1088551; 2001).

Yoshinaga teaches a pharmaceutical composition containing tamsulosin or a pharmaceutically acceptable salt thereof (page 3, paragraph [0013]; see present claims 1-2), particularly the hydrochloric acid salt (page 3, paragraph [0021]; see present claims 1-2), as a therapeutically effective dose for administration (page 3, paragraph [0014]; see present claims 1-2) for the treatment of voiding dysfunction associated with neurogenic bladder (abstract and page 3, paragraph [0014]; see present claims 1-2).

The functional limitation "for the therapy of overactive bladder" as recited at lines 1-2 of each of present claims 1-2 has been considered, but fails to impart any patentable moment to the composition since the physical and structural components of the presently claimed composition are identical to the physical and structural components of the prior art composition of Yoshinaga. Thus, such a recitation amounts to no more than an intended use of the presently claimed composition. In light of such, and absent factual evidence to the contrary, the composition of Yoshinaga is fully capable of performing the intended use as recited in the present claims.

Applicant's attention is drawn to the MPEP at §2111.02[R-2], which states, "During

examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art...***If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim.***" (emphasis added)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshinaga (EP 1088551; 2001) in view of Takeuchi et al. (EP 0801067; 1997).

Yoshinaga teaches a pharmaceutical composition containing tamsulosin or a pharmaceutically acceptable salt thereof (page 3, paragraph [0013]; see present claims 1-2), particularly the hydrochloric acid salt (page 3, paragraph [0021]; see present claims 1-2), as a therapeutically effective dose for administration (page 3, paragraph [0014]; see present claims 1-2) for the treatment of voiding dysfunction associated with neurogenic bladder (abstract and page 3, paragraph [0014]; see present claims 1-2).

The difference between the Yoshinaga reference and the presently claimed subject matter lies in that the reference fails to teach the use of a muscarinic receptor antagonist, such as quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate or its salts, as an effective component of the disclosed pharmaceutical composition.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate or its salts was known in the art to have efficacy in the treatment of neurogenic bladder and, thus, would have been useful for the same therapeutic objective of treating the voiding dysfunction associated with neurogenic bladder as disclosed by Yoshinaga.

In this regard, Takeuchi et al. (EP 0801067; 1997) is cited. Takeuchi et al. teaches quinuclidine derivatives or their salts as muscarinic (M3) receptor antagonists useful for the treatment of neurogenic bladder (page 4, lines 19-23), particularly the quinuclidine derivative 3-quinuclidnyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate (lines 2-3 of claim 8 at page 54; see also Examples 9-11 at pages 18-19).

Thus, in light of such a teaching, the use of the muscarinic receptor antagonist 3-quinuclidnyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate in the composition disclosed by Yoshinaga would have been *prima facie* obvious to one of ordinary skill in the art because it was well known in the art that such compounds both demonstrated efficacy in the treatment of neurogenic bladder and the symptoms and disorders associated with such a condition. Motivation to administer the muscarinic receptor antagonist 3-quinuclidnyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate flows logically from the efficacy demonstrated in the prior art as a potent compound useful for the treatment of neurogenic bladder. The skilled artisan would have reasonably concluded, in light of the shared efficacy shown by both tamsulosin and 3-quinuclidnyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate in treating neurogenic bladder, that a pharmaceutical composition comprising both components would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. It is further noted that in the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

II Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sellers et al. ("Potential Therapeutic Targets for Treatment of the Overactive Bladder", *World Journal of Urology*, 2001) in view of Caroon et al. (U.S. Patent No. 6,319,920; 2001) and Remington's Pharmaceutical Sciences (1980; pages 420-425).

Sellers et al. teaches the alpha-1-adrenoreceptor antagonist tamusolin as having activity in treating irritative symptoms (i.e., frequency, nocturia, urgency, etc.) in patients who do not

have significant bladder outlet obstruction (page 308, col.1, paragraph 3) and further discloses that alpha-1-adrenoreceptor antagonists relieve urgency and frequency in women, which is suggestive that such agents may have actions that influence bladder function that are in addition to their indirect effects via the prostate (page 308, paragraph bridging columns 1 and 2). Sellers et al. expressly states, "Thus, alpha-1-adrenoreceptor antagonists appear to influence bladder irritative symptoms via mechanisms additional to their effect on bladder outlet resistance...this groups of drugs would appear to have potential use in the treatment of the overactive bladder." (page 308, col.2, paragraph 2; see present claims 5-8)

The teachings of Sellers et al. are reasonably suggestive that the use of an alpha-1-adrenoreceptor antagonist, such as the disclosed antagonist compound tamsulosin, would have had efficacy in treating overactive bladder and the symptoms associated with such a condition. Furthermore, the context of the teachings of Sellers et al. is also reasonably suggestive that the compound(s) would have had efficacy in treating overactive bladder in the absence of a pathological factor, such as bladder outlet obstruction resulting from benign prostatic hypertrophy, since Sellers et al. expressly states that relief of symptoms in patients without significant bladder outlet obstruction was achieved using an alpha-1-adrenoreceptor antagonist.

Such a teaching is considered to be sufficient motivation supported by objective evidence that the use of the alpha-1-adrenoreceptor antagonist in the treatment of overactive bladder would have been *prima facie* obvious to the skilled artisan. Sellers et al. raise the reasonable expectation that such an agent would have success in treating such a condition. Applicant is reminded that express motivation to combine must not be explicitly stated in the prior art. Please reference MPEP §2145(X), which states, "However, there is no requirement that an "express,

written motivation to combine must appear in prior art references before a finding of obviousness."

The differences between the Sellers et al. reference and the presently claimed subject matter lies in that the references fails to teach the concomitant use of a muscarinic receptor antagonist as an effective component for the treatment of overactive bladder or the use of therapeutically effective amounts of the presently claimed active agents for the treatment of such a condition.

Muscarinic receptor antagonists were well known in the art to have efficacy in the treatment of overactive bladder and the symptoms associated with such a condition, such as urgency, frequency and urge incontinence, and, thus, would have been useful for the same therapeutic objective of treating overactive bladder as the alpha-1-adrenoreceptor antagonist (i.e., tamsulosin as disclosed by Sellers et al.

In this regard, Caroon et al. (U.S. Patent No. 6,319,920; 2001) is cited. Caroon et al. teaches 2-arylethyl-(piperidin-4-yl)methyl amine derivatives as muscarinic receptor antagonists useful for the treatment of genitourinary disorders, such as overactive bladder and the symptoms associated with such a condition (i.e., urgency, frequency, urge incontinence, etc.; col.1, lines 14-17 and col.27, lines 4-8).

Thus, in light of such a teaching, the use of a muscarinic receptor antagonist in combination with the alpha-1-adrenoreceptor antagonist (i.e., tamsulosin) as disclosed by Sellers et al. would have been *prima facie* obvious to one of ordinary skill in the art because it was well known in the art that such compounds both demonstrated efficacy in the treatment of overactive bladder and the urgency and frequency symptoms associated with such a condition. Motivation

to administer a muscarinic receptor antagonist in conjunction with the alpha-1-adrenoreceptor antagonist, tamsulosin, flows logically from the efficacy demonstrated in the prior art as a potent compound useful for the treatment of overactive bladder and the associated urgency and frequency symptoms. The skilled artisan would have reasonably concluded, in light of the shared efficacy shown by both tamsulosin and muscarinic receptor antagonists in treating such a condition, that a pharmaceutical composition comprising both components would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. It is further noted that in the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Moreover, the determination of the optimum therapeutically effective amounts to treat the condition of overactive bladder with the presently claimed active agent(s) would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the effective amounts that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed therapeutically effective amounts are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Lastly, the use of pharmaceutically acceptable salts of tamsulosin would also have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been obvious to the skilled artisan motivated by any one or more of these factors to formulate the active agent tamsulosin into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the agent itself.

Conclusion

Rejection of claims 1-8 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

December 9, 2005

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